

---

# **Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry**

## ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Oncology Center of Excellence (OCE)**

**August 2018  
Procedural**

# **Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry**

*Additional copies are available from:*

*Office of Communications, Division of Drug Information  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor  
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

*and/or*

*Office of Communication, Outreach, and Development  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Ave., Bldg. 71, rm. 3128  
Silver Spring, MD 20993-0002*

*Phone: 800-835-4709 or 240-402-8010; Email: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)  
<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Oncology Center of Excellence (OCE)**

**August 2018  
Procedural**

## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>2</b>
<b>III.</b>	<b>FIH EXPANSION COHORT DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES .....</b>	<b>3</b>
	<b>A. Definition of FIH Multiple Expansion Cohort Trials .....</b>	<b>3</b>
	<b>B. Potential Opportunities and Challenges Posed by FIH Multiple Expansion Cohort Trials ...</b>	<b>3</b>
<b>IV.</b>	<b>DRUG PRODUCT AND PATIENT CONSIDERATIONS .....</b>	<b>3</b>
<b>V.</b>	<b>CONSIDERATIONS BASED ON COHORT OBJECTIVES.....</b>	<b>4</b>
	<b>A. Confirming Safety of Recommended Phase 2 Dose .....</b>	<b>4</b>
	<b>B. Evaluating Preliminary Anti-Tumor Activity .....</b>	<b>4</b>
	<b>C. Evaluating Specific PK and Pharmacodynamic Aspects .....</b>	<b>5</b>
	<b>D. Further Dose/Schedule Exploration .....</b>	<b>6</b>
	<b>E. Biomarker Development .....</b>	<b>6</b>
	<b>F. Evaluating Drug Product Changes.....</b>	<b>7</b>
	<b>G. Evaluating More Than One Therapeutic Drug.....</b>	<b>8</b>
	<b>H. Evaluating PK, Tolerability, and Initial Evidence of Activity in the Pediatric Population ...</b>	<b>8</b>
<b>VI.</b>	<b>STATISTICAL CONSIDERATIONS .....</b>	<b>9</b>
<b>VII.</b>	<b>SAFETY CONSIDERATIONS .....</b>	<b>9</b>
	<b>A. Safety Monitoring and Reporting Plans .....</b>	<b>9</b>
	<b>B. Independent Safety Assessment Committee .....</b>	<b>10</b>
	<b>C. Institutional Review Board /Independent Ethics Committee .....</b>	<b>11</b>
	<b>D. Informed Consent Document.....</b>	<b>12</b>
<b>VIII.</b>	<b>PROTOCOL CONTENT.....</b>	<b>12</b>
	<b>A. Initial Protocol.....</b>	<b>13</b>
	<b>B. Protocol Amendments .....</b>	<b>13</b>
<b>IX.</b>	<b>COMMUNICATIONS AND INTERACTIONS WITH FDA .....</b>	<b>14</b>

1           **Expansion Cohorts: Use in First-In-Human Clinical Trials to**  
2           **Expedite Development of Oncology Drugs and Biologics**  
3           **Guidance for Industry<sup>1</sup>**  
4  
5  
6

7  
8           This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
9           Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
10          binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
11          applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
12          for this guidance as listed on the title page.  
13

14  
15  
16  
17          **I.       INTRODUCTION**  
18

19          The purpose of this guidance is to provide advice to sponsors regarding the design and conduct  
20          of first-in-human (FIH) clinical trials intended to efficiently expedite the clinical development of  
21          cancer drugs, including biological products, through multiple expansion cohort trial designs.<sup>2</sup>  
22          These are trial designs that employ multiple, concurrently accruing patient cohorts, where  
23          individual cohorts assess different aspects of the safety, pharmacokinetics, and anti-tumor  
24          activity of the drug. This guidance provides FDA’s current thinking regarding: (1)  
25          characteristics of drug products best suited for consideration for development under a multiple  
26          expansion cohort trial; (2) information to include in investigational new drug application (IND)  
27          submissions to support the use of individual cohorts; (3) when to interact with FDA on planning  
28          and conduct of multiple expansion cohort studies; and (4) safeguards to protect patients enrolled  
29          in FIH expansion cohort studies.  
30

31          This draft guidance is intended to serve as advice and as the starting point for discussions  
32          between FDA, pharmaceutical sponsors, the academic community, and the public.<sup>3</sup> This  
33          guidance does not address all issues relating to clinical trial design, statistical analysis, or the  
34          biomarker development process. Those topics are addressed in other guidances including the  
35          International Conference on Harmonisation guidances for industry *E9 Statistical Principles for*

---

<sup>1</sup> This guidance has been prepared by the Office of Hematology and Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* or *drug products* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

<sup>3</sup> In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during the development of cancer drugs.

***Contains Nonbinding Recommendations***  
***Draft — Not for Implementation***

36 *Clinical Trials and E10 Choice of Control Group and Related Issues in Clinical Trials* as well as  
37 the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.<sup>4</sup>  
38

39 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
40 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
41 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
42 the word *should* in Agency guidances means that something is suggested or recommended, but  
43 not required.  
44

45  
46 **II. BACKGROUND**  
47

48 Phase 1 clinical trials are designed to determine the metabolism and pharmacologic actions of an  
49 investigational drug in humans, the side effects associated with increasing doses, and, if possible,  
50 to gain early evidence of effectiveness.<sup>5</sup> The rationale for conducting phase 1 studies is to obtain  
51 sufficient information about the drug’s pharmacokinetic (PK) and pharmacologic effects to  
52 permit the design of subsequent well-controlled, scientifically valid safety and efficacy trials.  
53 The total number of patients included in phase 1 studies is anticipated to be in the range of 20 to  
54 80.  
55

56 FIH multiple expansion cohort trials are intended to expedite development by seamlessly  
57 proceeding from initial determination of a potentially effective dose to individual cohorts that  
58 have trial objectives typical of phase 2 trials (i.e., to estimate anti-tumor activity). These cohorts  
59 may be initiated before the analysis of the metabolism and pharmacokinetics of the  
60 investigational drug and with limited safety assessment. Such trials have enrolled between a few  
61 hundred to more than a thousand patients.<sup>6,7</sup> Because of the rapid enrollment and evolving  
62 nature of the information obtained in these trials, large numbers of patients are exposed to drugs  
63 with unknown efficacy and minimally characterized toxicity profiles. To mitigate such risks and  
64 to protect patients, it is imperative that sponsors establish an infrastructure to streamline trial  
65 logistics, facilitate data collection, and incorporate plans to rapidly assess emerging data in real  
66 time and to disseminate interim results to investigators, institutional review boards (IRBs), and  
67 regulators.  
68  
69

---

<sup>4</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>5</sup> 21 CFR 312.21(a)(1) and (2).

<sup>6</sup> KEYNOTE-001 study design at <https://clinicaltrials.gov/ct2/show/NCT01295827>.

<sup>7</sup> JAVELIN study design at <https://clinicaltrials.gov/show/NCT01772004>.

70 **III. FIH EXPANSION COHORT DEFINITION AND POTENTIAL**  
71 **OPPORTUNITIES AND CHALLENGES**

72  
73  
74

**A. Definition of FIH Multiple Expansion Cohort Trials**

75  
76  
77  
78  
79  
80  
81  
82  
83  
84

For the purpose of this guidance, an FIH multiple expansion cohort trial is an FIH trial with a single protocol with an initial dose-escalation phase that also contains three or more additional patient cohorts with cohort-specific objectives. The objectives of these expansion cohorts can include assessment of anti-tumor activity in a disease-specific setting, assessment of a reasonably safe dose in specific populations (e.g., pediatric or elderly patients or patients with organ impairment), evaluation of alternative doses or schedules, establishment of dose and schedule for the investigational drug administered with another oncology drug, or evaluation of the predictive value of a potential biomarker. In general, comparison of activity between cohorts is not planned except where a prespecified randomization and analysis plan are part of the protocol design.

85  
86  
87

**B. Potential Opportunities and Challenges Posed by FIH Multiple Expansion Cohort Trials**

88  
89  
90  
91

The principal advantage of conducting FIH multiple expansion cohort trials is efficiency in drug development, with the goal of making highly effective drugs widely available to the public as quickly as possible.

92  
93

FIH multiple expansion cohort studies pose several challenges and risks, including:

94  
95  
96  
97  
98  
99

- Challenges in disseminating new safety information to investigators, IRBs, and regulators in a timely manner. It is critical that investigators, IRBs, and regulators are updated with new safety information so that they can provide the necessary oversight for protection of human subjects and so that investigators can ensure that patients can provide adequate informed consent.

100  
101  
102

- Exposing a large number of patients across multiple, simultaneously accruing, cohorts to potentially suboptimal or toxic doses of an investigational drug.

103  
104

- Exposing more patients than required to achieve the cohort’s objectives.

105  
106  
107  
108

- Inefficient drug development based on *possibly missed interpretation* of preliminary trial results and unplanned analyses that can lead to delays in proper clinical development. For example, selection of dosage regimens or biomarker-selected populations based on unplanned between-cohort comparisons.

109  
110

**IV. DRUG PRODUCT AND PATIENT CONSIDERATIONS**

111  
112  
113  
114  
115

Given the potential for increased risks to patients posed by this trial design (see section III., FIH Expansion Cohort Definition and Potential Opportunities and Challenges), clinical trials with FIH multiple expansion cohorts should be limited to investigational drugs for indications and

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

116 patient populations in which the potential benefits justify the increased risks. To ensure that  
117 potential benefits outweigh the risks to patients, the patient population should be limited to  
118 patients with serious diseases for which no curative therapies are available. Sponsors should  
119 provide a robust rationale for use of an expansion cohort trial. As drug product development  
120 progresses, FDA expects that the investigational drug has the potential to meet the criteria for  
121 breakthrough therapy designation to support continuation of the expedited clinical development  
122 program,<sup>8</sup> such that the potential benefits of enrollment in these complex clinical protocols  
123 continue to outweigh the potential for the increased risks to patients.

124  
125 Drug product formulations containing drug substances with material attributes that allow for  
126 relatively straightforward bridging between early drug product formulations and marketing  
127 formulations (e.g., biopharmaceuticals classification system Class 1 designation, nonliposomal  
128 injections, and immediate release oral drug products) may be more appropriate for multiple  
129 expansion cohort trials.

130  
131 Characteristics of investigational drugs that are not suitable for study in clinical trials with  
132 multiple expansion cohorts because of increased risks of drug-related toxicity include steep  
133 toxicity indices and large inter- and intra-patient variability (i.e., co-efficient of variability  
134 greater than or equal to 100 percent) in pharmacokinetics indicative of polymorphic enzyme  
135 mediated drug clearance for small molecules.

136

137

### **V. CONSIDERATIONS BASED ON COHORT OBJECTIVES**

138

139  
140 Sponsors of FIH multiple expansion cohort trials should provide the scientific rationale for  
141 conducting each proposed cohort. To ensure that the objectives are met, a sponsor should  
142 carefully design key elements for each cohort, including specific endpoints, eligibility,  
143 monitoring plan, and statistical considerations to justify the sample size, in light of the available  
144 safety information. This information, as well as the information described in section VI.,  
145 Statistical Considerations, should be included in a new clinical protocol and subsequent protocol  
146 amendments adding one or more expansion cohorts.

147

#### **A. Confirming Safety of Recommended Phase 2 Dose**

148

149  
150 Expansion cohorts intended to further evaluate safety beyond the initial dose-escalation portion  
151 of a trial should be supported by detailed information on available safety and PK data from the  
152 dose-escalation phase and a summary of safety data from other expansion cohorts, if available.  
153 In situations where there is a narrow therapeutic index and dose-limiting toxicities may be fatal,  
154 expansion may need to be delayed until the recommended phase 2 dose is identified.

155

#### **B. Evaluating Preliminary Anti-Tumor Activity**

156

157  
158 Expansion cohorts assessing disease-specific cohort anti-tumor activity should include the  
159 following elements:

160

---

<sup>8</sup> See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 161 • A scientific rationale for inclusion of each population within a cohort based on proposed  
162 mechanism of action of drug and acceptability of risks in these proposed population(s)  
163 considering the natural history, underlying comorbidities, and susceptibility for adverse  
164 reactions due to tumor histology, as well as lack of satisfactory alternative therapy<sup>9</sup>  
165
- 166 • A statistical analysis plan for the cohort that includes justification of the maximum  
167 sample size and stopping rules for lack of activity, to minimize the number of patients  
168 exposed to an ineffective drug (e.g., generally limited to 40 patients with solid tumors  
169 based on a Simon 2-stage model<sup>10</sup> or 20 patients with hematological malignancies) where  
170 the rarity of the disease may support initiation of efficacy trials based on smaller efficacy  
171 databases  
172
- 173 • Updated safety experience from the dose-escalation portion and other expansion cohorts,  
174 as available<sup>11</sup>  
175

176 In general, based on the results observed in a disease-specific expansion cohort, a sponsor  
177 intending to continue development of a drug for that indication should submit a new IND to the  
178 appropriate review division to facilitate direct communication on the adequacy of the  
179 development program for that indication. If preliminary clinical evidence suggests a substantial  
180 improvement over available therapies on a clinically significant endpoint(s) in a patient  
181 population with a high unmet medical need, the sponsor should ask to meet with FDA to discuss  
182 further development (see section VIII., Protocol Content). In the exceptional situation where  
183 data from an expansion cohort may support a marketing application, the protocol should contain  
184 provisions ensuring adequate data quality, independent review of tumor-based endpoints, and  
185 optimal dose selection, as well as a prespecified plan ensuring statistical rigor.  
186

### **C. Evaluating Specific PK and Pharmacodynamic Aspects**

187  
188  
189 Expansion cohorts designed to evaluate the effect of food intake, organ dysfunction, and  
190 concomitant medications on the exposure to the investigational drug should be designed with  
191 knowledge of the preliminary pharmacokinetics and safety profile observed in the safety and  
192 dose-finding phase of the trial.  
193

- 194 • **Food effects**  
195
- 196 – PK trials in cancer patients should conform to the recommendations in the guidance  
197 for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies*  
198
  - 199 – PK studies enrolling healthy subjects to assess food effects should be conducted as  
200 separate clinical studies

---

<sup>9</sup> See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

<sup>10</sup> Simon, R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, *Controlled Clinical Trials*, Vol. 10, Issue 1, March, 1–10.

<sup>11</sup> 21 CFR 312.30(b).

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 201  
202     • **Organ dysfunction**  
203  
204         – Expansion cohort(s) studying organ dysfunction should conform to the  
205             recommendations in the draft guidance for industry *Pharmacokinetics in Patients*  
206             *With Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing*  
207             *and Labeling*<sup>12</sup> and the guidance for industry *Pharmacokinetics in Patients With*  
208             *Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and*  
209             *Labeling*

- 210  
211     • **Drug interactions**  
212  
213         – The dose and timing/sequence of the concomitant medications used in the cohort  
214             should be well-documented  
215  
216         – Drug interaction studies should conform to the recommendations in the draft  
217             guidance for industry *Clinical Drug Interaction Studies — Study Design, Data*  
218             *Analysis, and Clinical Implications*<sup>13</sup>

### **D. Further Dose/Schedule Exploration**

220  
221  
222 Sponsors of expansion cohort(s) intended to further assess optimal dose/schedule of the  
223 investigational drug should consider:

- 224  
225     • Randomization to two or more dosage regimens to increase the confidence that any  
226         differences between treatment arms are not due to chance alone  
227  
228     • Justification of sample size chosen to detect clinically important differences in safety and  
229         activity, if present  
230  
231     • Results of available safety, activity, and PK information to support the new proposed  
232         dosage(s)  
233  
234     • Results of exposure-response (safety and/or activity) modeling, if available, to justify  
235         new dosing regimens

### **E. Biomarker Development**

236  
237  
238  
239 Expansion cohorts evaluating biomarker-defined populations should employ in vitro diagnostic  
240 (IVD) assays that are analytically validated and should justify the use of the biomarker. Use of  
241 IVDs with inadequate performance characteristics (e.g., specificity, sensitivity) may produce  
242 spurious results and/or delay the development of a potentially effective drug. Sponsors should  
243 establish procedures for tumor sample acquisition, handling, and the testing and analysis plans as

---

<sup>12</sup> When final, this guidance will represent the FDA's current thinking on this topic.

<sup>13</sup> When final, this guidance will represent the FDA's current thinking on this topic.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

244 early as possible in the biomarker development program. FDA may ask for submission of the  
245 IVD's analytical validation data to determine whether the clinical results will be interpretable.  
246 The clinical validity of the exploratory biomarker(s) should be further evaluated in confirmatory  
247 trial(s).<sup>14</sup>

248  
249 If an IVD will be used for patient management (e.g., selection) in a clinical trial, the  
250 requirements for an investigational device exemption at 21 CFR part 812 must be assessed by the  
251 sponsor and IRBs. FDA recommends that sponsors contact the appropriate IVD review center  
252 (Center for Devices and Radiological Health or Center for Biologics Evaluation and Research)  
253 early in the development program to obtain a risk assessment of the device and further  
254 guidance.<sup>15</sup>

### **F. Evaluating Drug Product Changes**

256  
257  
258 The chemistry, manufacturing, and controls information submitted to support expansion cohort  
259 studies is expected to meet the level of detail appropriate for the stage of clinical  
260 development.<sup>16,17</sup>

261  
262 The sponsor should prominently identify in the cover letter of a protocol amendment any change  
263 that introduces into an ongoing trial a new formulation or presentation of a drug or major  
264 manufacturing changes. In such amendments, the sponsor should identify changes in drug  
265 product quality attributes that may require bridging to earlier clinical trial drug products that  
266 differ in their formulations, packaging configurations, manufacturing processes, and impurity  
267 profile to allow comparison of the clinical data across cohorts using different formulations.  
268 Expansion cohorts intended to bridge new and older formulations should have clear objectives  
269 and analysis plans for assessing differences in safety and pharmacokinetics. When changes in  
270 presentation result in significant modifications to dose preparation, human factors studies may be  
271 requested.<sup>18</sup> Depending on the effect of the changes, FDA may recommend that studies of new  
272 drug formulations be conducted under a new IND.

273  
274 Given the challenges in bridging formulation, presentation, or drug product manufacturing  
275 changes, FDA urges sponsors to meet with the review division to ensure that such expansion  
276 cohort(s) are adequately designed to meet the intended objective of bridging clinical data across

---

<sup>14</sup> See the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.

<sup>15</sup> See the draft guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>16</sup> See the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*.

<sup>17</sup> See the guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*.

<sup>18</sup> See the draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will represent the FDA's current thinking on this topic.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

277 cohorts. FDA may recommend additional clinical studies to bridge safety and efficacy data in  
278 support of a marketing application if drug product changes, such as formulation changes,  
279 production scale-up, manufacturing site changes, and manufacturing process changes during  
280 clinical development, are not adequately bridged. In the absence of such bridging information, it  
281 may not be scientifically valid to pool key clinical data and may significantly delay marketing  
282 approval.

### **G. Evaluating More Than One Therapeutic Drug**

286 Expansion cohort studies evaluating an investigational drug administered with an approved or  
287 another investigational drug should be initiated only after the preliminary safety profile and  
288 activity is characterized for each investigational drug as a single agent. The protocol for the  
289 expansion cohort trial should include the justification and scientific rationale for combining these  
290 drugs and a safety monitoring plan with attention to overlapping and potential synergistic  
291 toxicities.

293 For information regarding codevelopment of two investigational drugs as a fixed-dose  
294 combination drug product, see the guidance for industry *Codevelopment of Two or More New*  
295 *Investigational Drugs for Use in Combination*.

### **H. Evaluating PK, Tolerability, and Initial Evidence of Activity in the Pediatric Population**

300 Expansion cohorts evaluating pediatric populations should be strongly considered<sup>19</sup> if the drug  
301 has potential relevance for the treatment of one or more pediatric cancers based on the drug's  
302 mechanism of action. Appropriate investigational drugs include targeted drugs where the cell  
303 surface receptor, fusion protein, amplified or mutated gene, or cell signaling pathway drug  
304 effects are known to be responsible for the development or progression of one or more pediatric  
305 cancers. Prospective inclusion of one or more pediatric cohorts in a multiple expansion cohort  
306 trial, as an alternative to separate pediatric dose-finding and activity-estimating protocols,  
307 provides an opportunity to shorten the timeline to begin pediatric development. A description of  
308 studies containing pediatric expansion cohorts could be included as part of an initial pediatric  
309 study plan.

311 To ensure the prospect for direct clinical benefit from participation on a research study where  
312 there is a greater than minor increase over minimal risk,<sup>20</sup> sponsors should enroll pediatric  
313 patients in dose-finding and activity estimating cohorts after a reasonably safe dose and  
314 preliminary activity have been established in adults. In exceptional circumstances, substantive  
315 nonclinical evidence of activity in tumor-derived cell lines or patient-derived xenografts alone  
316 may provide sufficient justification for enrollment of a pediatric cohort before the availability of

---

<sup>19</sup> Section 505B(a)(1)(B) of the FD&C Act requires that all original NDAs or BLAs for a new active ingredient that are submitted on or after August 18, 2020, must “submit with the application reports on the investigation described in paragraph (3) if the drug or biological product that is the subject of the application is- (i) intended for the treatment of an adult cancer; and (ii) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.”

<sup>20</sup> 21 CFR 50.52.

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

317 full clinical data in adults. In these situations, sponsors should consider staged enrollment of  
318 older children or adolescents before younger children.

319  
320 Information to support expansion cohorts for pediatric patients should include detailed toxicity  
321 monitoring plans, plans for PK assessment, and, when appropriate, pharmacodynamic study  
322 objectives to guide further pediatric development. For targeted drugs, confirmation of the  
323 putative target’s presence should be documented and eligibility should be limited to pediatric  
324 patients with relapsed or refractory disease for whom no curative treatment exists.

325  
326 Further development of the drug for one or more pediatric cancer-specific indications should be  
327 pursued as a separate protocol.

328  
329

330 **VI. STATISTICAL CONSIDERATIONS**

331  
332 The background information for each expansion cohort should contain the scientific rationale for  
333 that individual cohort. Individual expansion cohorts should describe the prespecified stopping  
334 rules for that cohort, based on insufficient anti-tumor activity or unacceptable level of toxicity  
335 for that population. Finally, the analysis plan for each expansion cohort should contain adequate  
336 information justifying the planned sample size based on the cohort objectives; for those cohorts  
337 evaluating anti-tumor activity, the plans should specify the magnitude of anti-tumor activity that  
338 would warrant further evaluation of the drug. In a nonrandomized cohort, assessment of anti-  
339 tumor activity is generally determined using a Simon 2-stage design to limit exposure of  
340 additional patients to an ineffective drug.<sup>21</sup>

341  
342 The trial design for an individual cohort should ensure that the cohort’s trial objectives can be  
343 met. For example, sponsors should consider the need for randomization within a cohort for  
344 comparison of activity between different dosing regimens. In a cohort with a randomized design,  
345 the sample size and the inference that can be made will be based on the prespecified null and  
346 alternative hypotheses to be tested, the level of significance, and the power of the test.  
347 Comparisons between cohorts to which patients were not randomly assigned should be avoided.

348  
349

350 **VII. SAFETY CONSIDERATIONS**

351  
352 **A. Safety Monitoring and Reporting Plans**

353  
354 The sponsor is required to ensure proper monitoring of the investigations and to ensure that the  
355 investigations are conducted in accordance with the general investigational plan and protocols  
356 contained in the IND.<sup>22</sup>

357

---

<sup>21</sup> Simon, R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, *Controlled Clinical Trials*, Vol. 10, Issue 1, March, 1–10.

<sup>22</sup> 21 CFR 312.50. See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring*.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

358 The sponsor should establish a systematic approach that ensures rapid communication of serious  
359 safety issues, including plans for activation of protocol amendments to address serious safety  
360 issues, to clinical investigators and regulatory authorities under IND safety reporting  
361 regulations.<sup>23</sup>

362  
363 The IND should contain a proposed plan for submission of a cumulative summary of safety, on a  
364 periodic basis that is more frequent than annually.<sup>24</sup> New safety data that further identify,  
365 characterize, and provide insight on management of adverse reactions should be periodically  
366 assessed and submitted to the IND in support of modifications of one or more cohorts within the  
367 protocol.

368  
369 The interval for submission of cumulative safety reports should be agreed upon with FDA. The  
370 most recent cumulative safety report should be referenced in support of protocol amendments  
371 proposing modifications of existing or new expansion cohorts. Given the complexity of these  
372 trials and increased risks to patients, sponsors should select medical monitors who have training  
373 and experience in cancer treatment and clinical trials conduct.

374

### **B. Independent Safety Assessment Committee**

375

376  
377 An independent safety assessment committee (ISAC)<sup>25</sup> or an independent data monitoring  
378 committee (IDMC)<sup>26</sup> structured to assess safety in addition to efficacy should be established for  
379 all FIH multiple expansion cohort protocols, given that the complexity of these trials, with  
380 regards to different cohort objectives, trial populations, and dosages evaluated simultaneously,  
381 can lead to potential increased risks to patients. Responsibilities of the ISAC/IDMC should  
382 include, but not be limited to, analysis of incoming expedited safety reports, development of  
383 cumulative summaries of all adverse events, and making recommendations to the IND sponsor  
384 regarding protocol modifications to reduce risks to patients enrolled in the trial. The ISAC/  
385 IDMC should be charged with the real-time review of all serious adverse events<sup>27</sup> and meet  
386 periodically to assess the totality of safety information in the development program.<sup>28</sup> The  
387 ISAC/IDMC should have responsibility for performing prespecified and ad hoc assessments of  
388 safety and futility for each cohort, to recommend protocol modifications or other actions,  
389 including but not limited to:

390

- 391 • Changing the eligibility criteria if the risks of the intervention seem to be higher in a  
392 subgroup

---

<sup>23</sup> 21 CFR 312.32.

<sup>24</sup> 21 CFR 312.33.

<sup>25</sup> See the draft guidance for industry *Safety Assessment for IND Safety Reporting*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>26</sup> See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

<sup>27</sup> 21 CFR 312.32.

<sup>28</sup> See the draft guidance for industry *Safety Assessment for IND Safety Reporting*.

***Contains Nonbinding Recommendations***  
***Draft — Not for Implementation***

- 393
- 394
- 395
- 396
- 397
- 398
- 399
- Altering the drug product dosage and/or schedule if the adverse events observed appear likely to be reduced by such changes
  - Identifying information needed to inform current and future trial patients of newly identified risks via changes in the consent form and, in some cases, obtaining re-consent of current patients to continued trial participation

400

401 **C. Institutional Review Board /Independent Ethics Committee**

402

403 A clinical trial may not be initiated until it has been reviewed and approved by an

404 IRB/independent ethics committee, and it remains subject to continuing review by an IRB

405 throughout the duration of the trial.<sup>29</sup> To meet the continuing review requirements,<sup>30</sup> the

406 investigator should provide cumulative safety information provided by the IND sponsor to the

407 IRB along with other information required by the IRB.

408

409 Because of the complexity of expansion cohorts as discussed in section V.A., Confirming Safety

410 of Recommended Phase 2 Dose, the sponsor is generally expected to perform an assessment of

411 safety more frequently than an annual basis and provide this information to the investigator (see

412 section VII., Safety Considerations). Sponsors are required to “keep each participating

413 investigator informed of new observations discovered by or reported to the sponsor on the drug,

414 particularly with respect to adverse effects and safe use.”<sup>31</sup> The investigator is expected to

415 convey this information to the IRB at the time of continuing review, or sooner, if it is an

416 unanticipated problem involving risk to human subjects or others.<sup>32</sup> This summary information

417 may include: a description of the detailed plan for timely, periodic communication of trial

418 progress; cumulative safety information; and other reports from the ISAC/IDMC. This

419 information is necessary to allow the IRB to evaluate the risks to patients of the ongoing

420 investigation, the risks to patients of all protocol modifications (e.g., changes in dosing and

421 addition of new cohorts), and the adequacy of the informed consent document.

422

423 To facilitate IRB review of multicenter, FIH multiple expansion cohort trials, FDA recommends

424 the use of a central IRB as permitted.<sup>33,34</sup> The central IRB should have adequate resources and

425 appropriate expertise to review FIH multiple expansion cohort trials in a timely and thorough

426 manner. When necessary, an IRB may invite individuals with competence in special areas (i.e., a

---

<sup>29</sup> 21 CFR 56.103(a).

<sup>30</sup> 21 CFR 56.109(f).

<sup>31</sup> 21 CFR 312.55(b).

<sup>32</sup> See 21 CFR 312.66 and the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs — Improving Human Subject Protection*.

<sup>33</sup> 21 CFR 56.114.

<sup>34</sup> See the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials*.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

427 consultant) to assist in the review of complex issues that require expertise beyond or in addition  
428 to that available on the IRB.<sup>35</sup>

429  
430 Given the increased risks to patients participating in FIH multiple expansion cohort trials, IRBs  
431 should consider convening additional meetings (i.e., ad hoc meetings of an existing IRB) to  
432 review the evolving new safety information, provided regulatory requirements such as quorum  
433 can be met.<sup>36</sup> Alternatively, a separate, duly constituted specialty IRB can be established and  
434 specifically charged with meeting on short notice to review new information and/or  
435 modifications to FIH expansion cohort trials. Such an IRB would need to satisfy the same  
436 requirements of any IRB (i.e., 21 CFR part 56); however, it could be designed to facilitate  
437 quorum by keeping membership to a minimum (i.e., 21 CFR 56.107 requires that each IRB have  
438 at least five members) and being composed of experienced members who are capable of meeting  
439 and reviewing FIH multiple expansion cohort trial-related materials on short notice. Ad hoc  
440 meetings of an existing IRB or the establishment of a separate specialty IRB designed to  
441 facilitate the review of FIH multiple expansion cohort trials are acceptable approaches that, if  
442 appropriately constituted and operated, can satisfy the regulatory requirement for IRB oversight.  
443

### **D. Informed Consent Document**

444  
445  
446 Informed consent documents should be updated as new information is obtained during the trial  
447 that may affect a patient's decision to participate in or remain in the trial. FDA may request  
448 submission of the original and all updated informed consent forms to the IND to permit an  
449 evaluation of whether patients have the information to make informed decisions regarding  
450 participation in the trial.

451  
452 In addition, the informed consent document should be updated to reflect all clinically important  
453 protocol modifications. Amendments to FIH multiple expansion cohort trials should be  
454 submitted to the IND before implemented, unless immediate modifications should be submitted  
455 for patient safety. The updated consent document should be submitted in each IND amendment  
456 containing clinically important protocol modifications.

457  
458

## **VIII. PROTOCOL CONTENT**

459  
460  
461 FIH multiple expansion cohort protocols should contain all of the elements for clinical  
462 protocols;<sup>37</sup> however, sponsors should consider whether there is a need for a greater level of  
463 detail to allow FDA and others (investigators, IRBs) to ensure that the risks to patients are not  
464 unreasonable and that the goals for each expansion cohort are clear and can be met. In addition,  
465 FDA expects that such INDs will be submitted in an electronic format (i.e., electronic common  
466 technical document).

467

---

<sup>35</sup> 21 CFR 56.107(f).

<sup>36</sup> 21 CFR 56.108(c).

<sup>37</sup> 21 CFR 312.23(a)(6)(iii).

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

468 This trial design presents challenges in patient oversight caused by rapid enrollment in a large  
469 number of patients exposed to the investigational drug. Safety information may not be readily  
470 available, which may expose patients to higher potential risks and may be unethical if the trial is  
471 not carefully planned to adequately address the specific scientific objectives of each expansion  
472 cohort. Therefore, failure to provide sufficient detail, either in the initial protocol or in protocol  
473 amendments, on the goals and conduct of the clinical protocol in a well-defined population  
474 where the risks may be acceptable can result in the trial being placed on clinical hold.  
475

### **A. Initial Protocol**

476  
477  
478 The initial IND submission containing an FIH multiple expansion cohort protocol should contain  
479 all of the information described in sections V., VI., and VII.<sup>38</sup> Additionally, the protocol and  
480 IND should contain:

- 481  
482 • A detailed, clearly identified table of contents and protocol section headers indicating the  
483 dosage regimen and dose modifications for each discrete cohort, to avoid medication  
484 errors when treatment plans differ by cohort (dose-escalation versus dose-expansion and  
485 between individual expansion cohorts, if applicable)  
486
- 487 • A schema for the data flow (data collection, analysis, and dissemination in real time)  
488
- 489 • A description of the plan for submission of interim safety and efficacy results to FDA,  
490 other groups responsible for monitoring patient safety (e.g., IRB, ISAC, IDMC), and  
491 investigators, to ensure that the risks to patients are mitigated  
492

### **B. Protocol Amendments**

493  
494  
495 Protocol amendments that substantively affect the safety or scope of the protocol should contain  
496 a clean version of the amended protocol, a copy of the protocol with tracked changes, and the  
497 following supportive information, if available:<sup>39</sup>  
498

- 499 • A summary of the available adverse reaction profile observed, by dose and schedule for  
500 patients with adequate evaluation (i.e., patients that have completed at least one treatment  
501 cycle with submission of safety information to the sponsor)  
502
- 503 • New nonclinical toxicology or pharmacology data, and supportive clinical data as  
504 appropriate to support the protocol modification  
505
- 506 • An updated informed consent document  
507  
508

---

<sup>38</sup> See 21 CFR 312.23 for IND content and format requirements.

<sup>39</sup> See 21 CFR 312.30(d) and 312.31(b) for content and format requirements for protocol amendments and information amendments.

*Contains Nonbinding Recommendations*  
*Draft — Not for Implementation*

509 **IX. COMMUNICATIONS AND INTERACTIONS WITH FDA**  
510

511 For all communication with FDA, sponsors and FDA should consult the guidance for industry  
512 and review staff *Best Practices for Communication Between IND Sponsors and FDA During*  
513 *Drug Development*.  
514

- 515 • Sponsors should request a pre-IND meeting to discuss their plans to conduct an FIH  
516 multiple expansion cohort trial. When the original IND is submitted, the cover letter  
517 should prominently identify it as an FIH multiple expansion cohort trial.  
518
- 519 • The sponsor should also notify the regulatory project manager via secure email or  
520 telephone call 48 hours before submission of any protocol amendment that substantively  
521 affects the safety or scope of the protocol.  
522
- 523 • Though an amended protocol may proceed upon submission to the IND, FDA strongly  
524 encourages sponsors to submit amendments at least 30 days before planned activation of  
525 the amendment to allow FDA to conduct a safety review. Amendments containing  
526 changes the sponsor considers necessary to ensure patient safety (e.g., closure of a cohort  
527 for unacceptable toxicity, modification of eligibility, or monitoring to mitigate the risks  
528 of adverse reactions) *should be implemented immediately and submitted as soon as*  
529 *possible*.  
530
- 531 • Either FDA or sponsors may request a teleconference to discuss protocol amendments  
532 within 30 days of their submissions to the IND. Further development in specific patient  
533 populations should be discussed with FDA in a formal meeting.<sup>40</sup>

---

<sup>40</sup> See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent the FDA's current thinking on this topic.